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Original Article

Chronic hepatitis B infection and risk of antituberculosis drug-induced liver injury: Systematic review and meta-analysis

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Abstract

Background: Antituberculosis drug-induced liver injury (ATDILI) is a major safety concern for the treatment of tuberculosis (TB). The impact of chronic hepatitis B infection (CHBI) on the risk of ATDILI is still controversial. In this study, we aimed to assess systematically the influence of CHBI on the susceptibility to ATDILI.

Methods: We reviewed all English-language medical literature with the medical subject search headings *hepatitis B* and *antitubercular agents* from the major medical databases. Thereafter, a systematic review and meta-analysis was performed on those publications that qualified.

Results: A total of 938 citations were retrieved on the initial major database search, from which 15 studies were determined to be eligible for analysis. While undergoing anti-TB treatment, 575 cases with drug-induced liver injury (DILI) and 4128 controls without DILI were enrolled into this analysis. The pooled odds ratio of all studies for the CHBI to ATDILI was 2.18 (95% confidence interval, 1.41−3.37). Among the studies with a strict definition of DILI (alanine aminotransferase > 5 × upper limit of normal value) and combination anti-TB regimen, the impact of CHBI on ATDILI was significant only in the prospective studies (odds ratio, 3.41; 95% confidence interval, 1.77−6.59), but not in the case−control studies. However, in the studies with a strict definition of DILI and isoniazid only treatment, the association between CHBI and ATDILI was not statistically significant.

Conclusion: This meta-analysis suggests that CHBI may increase the risk of ATDILI in the standard combination therapy for active TB. Close follow-up and regular liver test monitoring are mandatory to treat TB in chronic hepatitis B carriers.

Keywords: drug-induced liver injury; hepatitis B; meta-analysis; tuberculosis

1. Introduction

There has been a resurgence of tuberculosis (TB) as a public health burden and challenge arising from the increasing prevalence of drug-resistant *Mycobacterium tuberculosis* strains and patients with AIDS.[1,2] The three common first-line drugs for TB, isoniazid, rifampicin, and pyrazinamide, have the potential to induce liver injury.[1−4] This anti-TB drug-induced liver injury (ATDILI) ranges from mild to severe forms, and can even be fatal.[1−4] The incidence of ATDILI

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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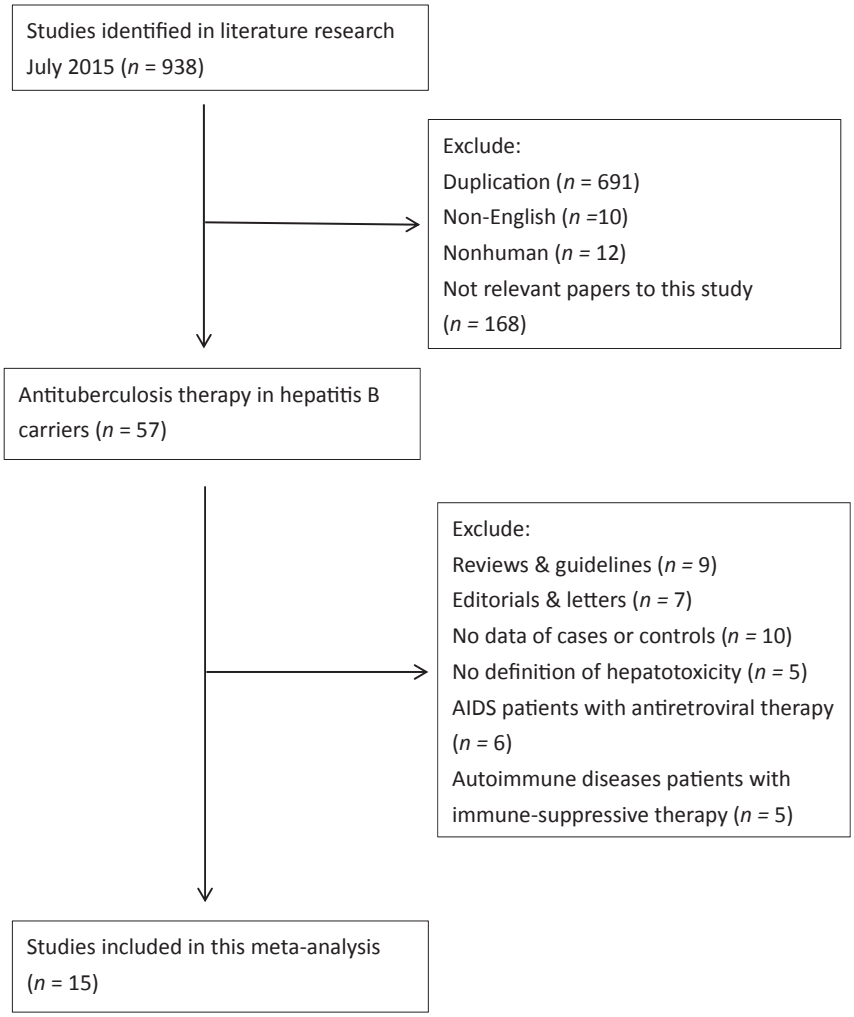

Fig. 1. Flow chart of the selection of eligible studies.

depends on different anti-TB regimens, definitions of liver injury, and ethnic populations. Generally, 10–20% of patients may have elevated serum aminotransferase during the period of treatment.[1–3] Around 1% of patients may develop overt hepatitis, defined as significant elevation of serum aminotransferase, with jaundice or other clinical symptoms/signs. The mortality rate of patients with overt hepatitis is estimated to be around 10%.[1–3] ATDILI is the most prevalent drug-induced liver injury (DILI) in Taiwan, China, India, South Africa, and many other areas, which can both threaten patients' health and hinder the treatment of TB.[1–3] Therefore, reasonable attempts to militate against this hepatotoxicity are important.

A better understanding of risk factors of ATDILI may assist in the prevention and management of this crucial adverse drug reaction.[5,6] Elderly, Asian, malnutrition, alcoholism, chronic hepatitis B and C infections, AIDS, pregnancy, coadministration of hepatotoxic agents, abnormal baseline liver function, and genetic factors have been reported to increase the risk of ATDILI.[1–8] Chronic hepatitis B infection (CHBI) is prevalent in Asia, and the interaction of CHBI and ATDILI has been a concern for many decades. Some studies suggest CHBI may increase the incidence and severity of ATDILI.[9–15] However, many recent studies, most of them prospective studies from Asia, have challenged this association.[16–24] Based on the earlier studies, the guidelines of anti-TB treatment in the USA, Taiwan, and many other countries have regarded CHBI as a risk factor, and suggested regular monitoring liver biochemical tests in TB patients with CHBI before and during the period of anti-TB treatment.[4,25] This suggestion is based on the assumption that CHBI may increase the risk of ATDILI. However, all the relevant studies are small in sample size, with inconsistent results. Currently, this crucial issue remains controversial. We, therefore, performed a systematic review and meta-analysis to examine the association between CHBI and the risk of ATDILI.

2. Methods

2.1. Identification and retrieval of studies

We performed a search of Medline, PubMed, Embase, and the Cochrane Database of Systemic Review for full-length English language articles examining the association of

Table 1
Main characteristics of the 15 included studies in the order of publication year.

1st author, y[ref]	Publication country	Race	Sex (M/F)		Age (y) mean ± SD		Study design	Sample size (case/control)	Anti-TB regimen	Main diagnostic criteria of DILI	OR of DILI in HBV (95% CI)
			HBV (+)	HBV (−)	HBV (+)	HBV (−)					
McGlynn, 1986[14]	USA	Asian	ND	ND	ND	ND	Prospective	20/361	Isoniazid	ALT > ULN	4.19 (1.66−10.55)*
Hwang, 1997[16]	Taiwan	Asian	6/3	40/14	40 ± 5	44 ± 2	Prospective	63/177	4 combination	ALT > ULN	1.17 (0.51−2.71)
Wong, 2000[10]	Hong Kong	Asian	33/10	171/105	45 ± 16	46 ± 19	Prospective	41/319	4 combination	ALT > 1.5 ULN	6.00 (2.85−12.62)*
Patel, 2002[11]	USA	Asian	61/42	23/20	ND	ND	Prospective	3/155	Isoniazid	ALT > 5 ULN	13.80 (0.70−272.2)
Fernández-Villar, 2003[17]	Spain	Caucasian	ND	ND	ND	ND	Prospective	20/402	Isoniazid	ALT > 5 ULN	1.11 (0.06−19.89)
Pan, 2005[15]	China	Asian	ND	ND	ND	ND	Prospective	53/62	4 combination	ALT > 5 ULN	6.37 (2.18−18.62)*
Lee, 2005[18]	Korea	Asian	58/52	58/39	44 ± 15	44 ± 16	Case−control	13/194	4 combination	ALT > 3 ULN	2.07 (0.62−6.95)
Sun, 2009[12]	Taiwan	Asian	ND	ND	ND	ND	Prospective	48/228	4 combination	ALT > 5 ULN	3.89 (1.31−11.59)*
Chien, 2010[19]	Taiwan	Asian	19/6	173/97	61 ± 15	65 ± 20	Case−control	28/292	4 combination	ALT > 5 ULN	1.54 (0.43−5.54)
Wang, 2011[13]	Taiwan	Asian	29/13	184/110	>65; 31%	>65; 41%	Prospective	64/314	4 combination	ALT > 5 ULN	2.13 (0.99−4.56)
Chan, 2012[20]	Taiwan	Asian	ND	ND	ND	ND	Prospective	5/158	Isoniazid	ALT > 3 ULN	0.60 (0.03−11.34)
Shu, 2013[21]	Taiwan	Asian	ND	ND	ND	ND	Case−control	118/888	4 combination	ALT > 5 ULN	0.68 (0.31−1.53)
Lomtadze, 2013[22]	USA	Caucasian	ND	ND	ND	ND	Prospective	59/241	4 combination	ALT > 2 ULN	3.31 (1.01−10.86)*
Shen, 2014[23]	China	Asian	ND	ND	ND	ND	Case−control	54/206	4 combination	ALT > 3 ULN	1.99 (0.95−4.19)
Liu, 2014[24]	Taiwan	Asian	61/14	281/111	62 ± 15	69 ± 18	Case−control	42/425	4 combination	ALT > 5 ULN	0.64 (0.24−1.69)

*$p < 0.05$.
ALT = alanine aminotransferase; CI = confidence interval; DILI = drug-induced liver injury; HBV(+) = hepatitis B virus carrier; HBV(−) = non-hepatitis B virus carrier; ND = no data; OR = odds ratio; TB = tuberculosis; ULN = upper limit of normal value.

CHBI and ATDILI. The medical subjects heading search terms were *hepatitis B/hepatitis B*, *chronic*, and *antitubercular agents*. All databases were searched from their inception up to July 2015. Articles were selected for full text based on title and abstract. Additionally, a manual search of the bibliographies of retrieved publications was done to increase the yield of potentially relevant articles. Two investigators independently assessed the titles and abstracts of all retrieved papers and assessed their eligibility for the study. Differences in opinion were resolved by consensus with the other three investigators.

2.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria were defined at the time of study conception and before data collection. For inclusion into the meta-analysis, a study had to: (1) include patients with anti-TB treatment; (2) recruit patients with or without ATDILI, and with or without CHBI; and (3) be published as a full-length article. We excluded studies: (1) without definition of ATDILI; (2) involving patients with AIDS and undergoing antiretroviral therapy; (3) patients with autoimmune diseases and taking immunomodulators, such as prednisolone, methotrexate, and tumor necrosis factor-α blockers. Studies included in the analysis were reviewed for the following characteristics: author and year of publication; ethnicity; prospective or retrospective study; anti-TB regimen; and definition of ATDLI.

2.3. Statistical analysis

The odds ratio (OR) and 95% confidence interval (CI) for the association of incidence of ATDLI and CHBI were analyzed. The random effects model was applied for analyzing the pooled data. Heterogeneity was tested by the between-study variance using the I^2 statistics with a cutoff of $\geq 50\%$, and χ^2 test for Cochran Q statistics with $p < 0.10$. Subgroup analysis was performed if heterogeneity existed, and funnel plots were used to assess the extent of publication bias. All statistical analyses were performed using the Review Manager version 5.3.5 (RevMan for Windows, 2015; The Cochrane Collaboration, Oxford, UK).

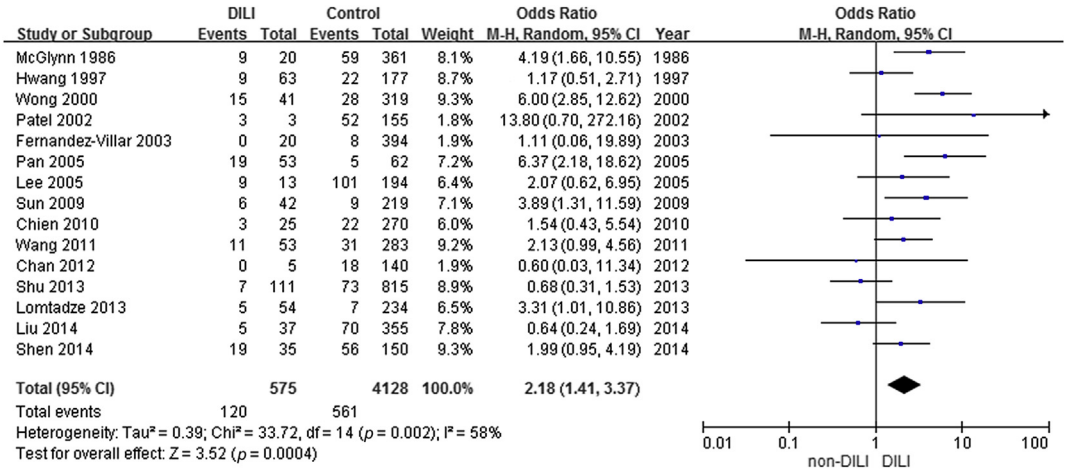

Fig. 2. Forest plot of association between chronic hepatitis B infection and the risk of antituberculosis drug-induced liver injury in all 15 studies. Events denote patients with chronic hepatitis B infection. CI = confidence interval; DILI = drug-induced liver injury; M-H = Mantel–Haenszel.

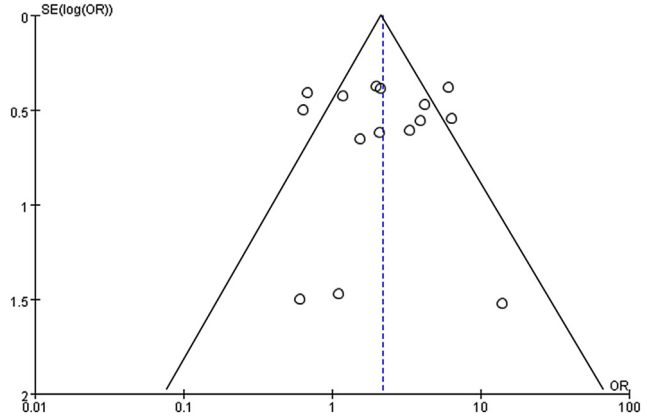

Fig. 3. Funnel plot for the assessment of publication bias.

3. Results

A total of 938 citations were retrieved pursuant to the initial search. After excluding unqualified papers, a total of 15 studies were included in the meta-analysis (Fig. 1). The baseline characteristics of the included studies are reported in Table 1. Overall, for patients who had undergone anti-TB treatment, 575 patients with drug-induced liver injury (DILI) and 4128 controls were enrolled into this study. A total of 13 studies were based on the study of East Asian patients, and only two studies focused on Caucasians (Table 1). Ten of the 15 studies were prospective studies, while five were retrospective case–control studies. Eleven of these studies recruited patients with active TB, undergoing the standard treatment of four-drug combination therapy, but four studies focused on patients with latent TB and ongoing isoniazid single-drug prophylactic treatment. Eight of the 15 studies adopted the major diagnostic criteria of DILI as serum alanine aminotransferase (ALT) more than five times the upper limit of normal value (ULN), which is a strict definition of DILI.

The OR of all included studies of the CHB status in the risk of ATDILI was 2.18 (95% CI 1.41–3.37; Fig. 2). There was significant heterogeneity among the studies (I^2 = 58%, p = 0.002).However, no significant publication bias was detected by funnel plot (Fig. 3).

Among the studies utilizing the strict definition of DILI (ALT > 5 × upper limit of normal value) and combination anti-TB regimen, the impact of CHBI on ATDILI was significant only in the prospective studies (OR, 3.41; 95% CI, 1.77–6.59), but not in the case–control studies (Fig. 4). However, in the studies using the strict definition of DILI and isoniazid-only treatment, the association between CHBI and ATDILI was not statistically significant (Fig. 5).

4. Discussion

TB and CHBI may occur in the same individual, and it is suspected that patients with CHBI may have an elevated risk of ATDILI. This meta-analysis has shown that hepatitis B virus (HBV) carriers have a predilection for ATDL in the standard combination therapy to active TB.

Identification of high risk patients with ATDILI is crucial in the prevention of this potentially fatal DILI. Several decades ago, a few studies noted the association of CHBI and ATDILI.[9–15] One of those studies was our retrospective investigation, which demonstrated that HBV carriers had a higher incidence of ATDILI than noncarriers; also, it was noted that HBV carriers with ATDILI had more severe liver injury compared with noncarriers with ATDILI.[9] Although this study represented a pioneering undertaking in this field, it was not included into this meta-analysis because the CHB status data were not available in the non-ATDILI group.[9]

One prospective study from Hong Kong highlights that the incidence of liver dysfunction was significantly higher in HBV carriers given anti-TB drugs (34.9%), compared with non-carriers given anti-TB drugs (9.4%) and HBV carriers not given anti-TB drugs (8.1%).[10] After excluding patients with

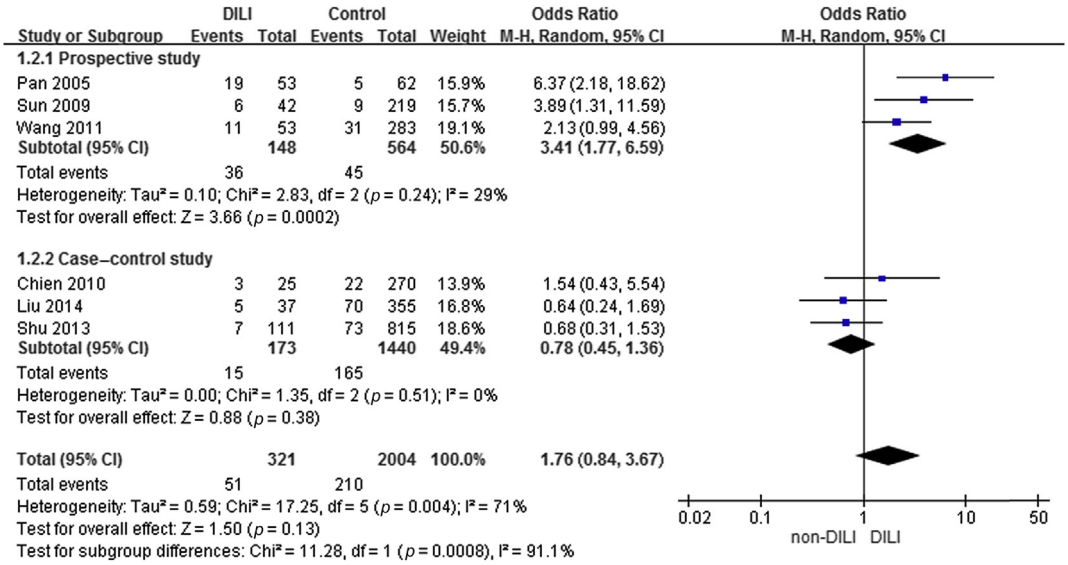

Fig. 4. Odds ratio of chronic hepatitis B infection to antituberculosis drug-induced liver injury by the subgroup analysis of prospective studies and case–control studies in those with strict definition of DILI (ALT > 5 times the upper limit of normal value) and four-drug combination anti-TB regimen. Events denote patients with chronic hepatitis B infection. CI = confidence interval; DILI = drug-induced liver injury; M-H = Mantel–Haenszel.

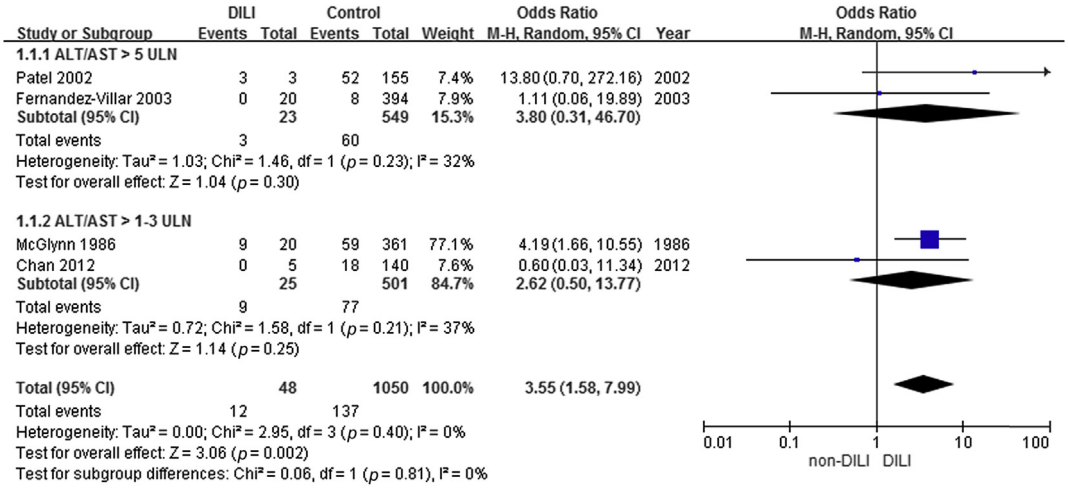

Fig. 5. Odds ratio of chronic hepatitis B infection to antituberculosis drug-induced liver injury by the subgroup analysis of different diagnostic criteria in those with isoniazid only treatment. Events denote patients with chronic hepatitis B infection. CI = confidence interval; DILI = drug-induced liver injury; M-H = Mantel–Haenszel.

elevated pretreatment ALT levels and those who developed hepatitis B e antigen seroconversion, the first group still had a high incidence of liver dysfunction (26.3%). After a review of evidence derived from laboratory and histology data, they also found that this group had more severe liver injury than the other two control groups. Although this study could not completely rule out the role of HBV flare-up in ATDILI, the authors believed CHBI is an independent risk factor for this hepatotoxicity.

However, it would appear that several recent studies have discrepant results.[16–24] The diverse HBV activity and liver reserve in HBV carriers may influence the susceptibility and severity of DILI. Positive serum hepatitis B e antigen (HBeAg) and high HBV-DNA represent high activity and infectivity of HBV, which may cause more hepatic damage to the host. Under these circumstances, this cohort of HBV carriers may have less liver reserve to dispose of anti-TB drugs, and thus render a higher incidence and severity of DILI. Patel and Voigt[11] first demonstrated that only the positive HBeAg HBV carriers have a higher risk of ATDILI. Wang et al[13] further showed that only the HBV carriers with high viral load (HBV-DNA) have an increased susceptibility to ATDILI. Therefore, it is plausible that the activity of HBV may play an important role in the development of ATDILI. However, data involving HBeAg and HBV-DNA are lacking in most of the relevant studies. Further large scale control trials, including information about HBV activity, are mandatory to corroborate this association.

Patient ethnicity may influence the susceptibility of DILI. However, in this meta-analysis, 13 studies involved the use of Asian individuals, while only two studies focused on Caucasians. Therefore, the minimal number of Caucasian studies involved rendered meaningless any further analysis of the impact of ethnicity.

However, this meta-analysis did further verify the reliability of prospective cohort study (Fig. 4). It is possible that the number of DILI cases may be underestimated, without regular monitoring of liver tests in the case–control studies.

The definition of DILI may affect study outcomes, and there remains ongoing debate as to an adequate definition of DILI. According to criteria from the Council for International Organizations of Medical Sciences, ALT/aspartate transaminase (AST) more than two times the level of ULN is regarded as DILI.[26] However, a mild increase of ALT/AST may have no clinical significance. Elevation of ALT/AST more than five times ULN, or more than three times ULN with jaundice, was suggested as the inclusion criteria of DILI by the US DILI Network.[27,28] The higher threshold of ALT/AST may select real DILI patients, who deserve further management, such as discontinuing or decreasing dose of discriminated drugs, close monitoring liver function, and liver transplantation if necessary. We adopted the strict diagnostic criteria of the DILI Network, and found that the impact of CHBI on ATDILI was still significant in the prospective studies with four-drug combination therapy (Fig. 4). By contrast, in those studies using the strict definition of DILI and isoniazid-only treatment, the association between CHBI and ATDILI was not statistically significant. It is reasonable to infer that the isoniazid-only therapy is less toxic than the four-drug combination anti-TB regimen, which renders the interaction with HBV insignificant.

The reason why HBV carriers have a higher risk of ATDILI remains to be elucidated. However, several explanations have been proposed, including a suspicion about reactivation of HBV with flare-up hepatitis, and which has manifested with high HBV-DNA and positive HBeAg in some patients as mentioned.[11,13] However, many HBV carriers with liver dysfunction had negative HBeAg, and low or undetectable HBV-DNA, whose hepatic damage could not be attributed to HBV.[10] In addition, in Wong et al's[10] study, the HBV carriers with anti-TB treatment still had a higher incidence of liver injury than the HBV carriers without anti-TB therapy in the same follow-up period. Therefore, reactivation of HBV can only explain the cause of liver dysfunction in a portion of the cases. Another possibility is that an improved immune system due to TB infection control may lead to an attack on the intrahepatocytic HBV.[1] Additionally, in HBV carriers, liver dysfunction may impair the metabolism of anti-TB drugs, resulting in the accumulation of more toxic metabolites. In addition to less liver reserve in HBV carriers, these metabolites may easily further damage the liver. Furthermore, patients with CHBI may have an upregulation of cytokines and a mixed inflammatory response. This proinflammatory condition triggered by replicating HBV may increase the susceptibility to toxic metabolites from anti-TB drugs.[11] However, the true mechanism and interaction of HBV and anti-TB drugs in hepatotoxicity remains unknown, which requires further basic study to elucidate.

The limitations of this meta-analysis are that we excluded those studies focusing on patients with AIDS and autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and Crohn's disease. Therefore, the conclusion reached in this study could not be extrapolated significantly to these other patient groups. The reason we excluded AIDS patients is that these patients are always under long-term antiretroviral therapy, which may also induce liver injury. It is difficult to identify whether liver dysfunction is caused by anti-retroviral agents, anti-TB drugs, or reactivation of HBV. Similarly, the patients with autoimmune diseases may have coadministration with many immuno-modulators or anti-inflammatory drugs, such as prednisolone, methotrexate, tumor necrosis factor-α blocker, sulfa drugs, and nonsteroid anti-inflammatory drugs. All of these agents may induce liver injury, and some of them may prompt HBV reactivation. To avoid complexity and uncertainty, we excluded all of these relevant papers. It may be possible to analyze these patient groups when more studies are available in the future. The other limitation of this meta-analysis is that all the studies could not completely rule out the possibility of acute exacerbation of CHBI in HBV carriers, alcoholic liver disease and nonalcoholic fatty liver disease in the liver dysfunction, although the strict diagnostic criteria of DILI may exclude some patients with alcoholic liver disease and nonalcoholic fatty liver disease.

To prevent ATDILI, regular monitoring liver tests was strongly suggested by the Center for Disease Control, Taiwan, for all TB patients which included assaying liver biochemical tests prior to anti-TB treatment, and at the 2nd week, 4th week, and 8th week after treatment.[25] Thereafter, the necessity and frequency of monitoring will depend on the status of chronic viral hepatitis infection and the clinical condition of the patients. In the USA, monitoring of liver tests is recommended for high-risk groups only, such as patients with chronic viral hepatitis infection, AIDS, chronic ethanol consumption, and pregnant women.[4] This can be attributed to the relatively low incidence of ATDILI in the USA, compared with that in Taiwan and many other countries. A national 12-year case analysis in Taiwan revealed that patients without liver test monitoring had more severe liver injuries and poorer outcomes than those with regular liver test monitoring.[29] Since the present meta-analysis supports the association of CHBI and ATDILI, we underline the importance of regular monitoring of liver biochemical tests before and during anti-TB treatment in HBV carriers.

In conclusion, this meta-analysis revealed that CHBI may increase the risk of ATDILI in standard combination therapy for active TB. Furthermore, our results underscore the importance of close monitoring liver tests in HBV carriers during anti-TB treatment.

Acknowledgments

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